

WO 2004/016607

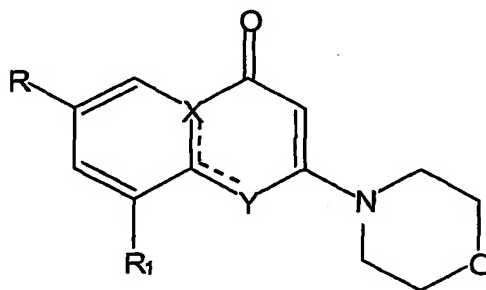
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ART 34 AMDT

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**WE CLAIM:**

1. A method of disrupting platelet aggregation and adhesion occurring under high shear cpnditions comprising administering an effective amount of a selective PI 3-kinase inhibitor to a patient in need thereof.
2. A method for antithrombosis comprising administering an effective amount of a selective PI 3-kinase  $\beta$  inhibitor to a patient in need thereof, provided that the inhibitor is not according to formula (II):



(II)

wherein,

R is H, OH, F, Cl, Br, I, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl or (CH<sub>2</sub>)<sub>n</sub>-aryl;

R<sup>1</sup> is H, OH, F, Cl, Br, I, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, CH=CH-aryl, C≡C-aryl, (CHR<sup>3</sup>)<sub>n</sub>-aryl, NR<sup>3</sup>-C<sub>1</sub>-C<sub>6</sub> alkyl, NR<sup>3</sup>-cycloalkyl, NR<sup>3</sup>-(CHR<sup>3</sup>)<sub>n</sub>-aryl, (CHR<sup>3</sup>)<sub>n</sub>-NR<sup>3</sup>-alkyl, (CHR<sup>3</sup>)<sub>n</sub>-NR<sup>3</sup>-cycloalkyl, (CHR<sup>3</sup>)<sub>n</sub>-O-aryl, (CHR<sup>3</sup>)<sub>n</sub>-O-alkyl, (CHR<sup>3</sup>)<sub>n</sub>-O-cycloalkyl, O-(CHR<sup>3</sup>)<sub>n</sub>-aryl, S-(CHR<sup>3</sup>)<sub>n</sub>-aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO<sub>2</sub>H, CO<sub>2</sub>R<sup>3</sup>, NO<sub>2</sub>, CF<sub>3</sub>, substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF<sub>3</sub>, OR<sup>3</sup>, OSO<sub>2</sub>-aryl, substituted or unsubstituted amine, NHCOR<sup>3</sup>, NHSO<sub>2</sub>R<sup>3</sup>, CONHR<sup>3</sup>, or SO<sub>2</sub>NHR<sup>3</sup>; and

R<sup>3</sup> is H, or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>alkyl, substituted or unsubstituted aryl; except where the compound of formula (II) is selected from the group consisting of: 9-(3-pyridinylmethyl)oxy-2-morpholinyl-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-140);

7-methyl-9-phenylaminomethyl-2-morpholinyl-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-183);

8-(4-methylphenyl)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-113);

8-(4-fluorophenoxy)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-121);

2-morpholinyl-8-(phenylmethyl)-4H-1-benzopyran-4-one (TGX-90);

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2-(4-morpholinyl)-8-(4-fluoro-2-methylphenyl)oxy-4H-1-benzopyran-4-one (TGX-184);

9-[(2-chlorophenyl)-methyl]amino-7-methyl-2-(4-morpholinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-167);

9-[(2-methoxyphenyl)-methyl]amino-7-methyl-2-(4-morpholinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-137);

7-methyl-2-(4-morpholinyl)-9-[(phenylmethyl)amino]-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-126);

9-[(4-fluoro-2-methylphenyl)amino]-7-methyl-2-(4-morpholinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-170);

7-methyl-2-(4-morpholinyl)-9-[(1R)-1-phenylethyl]amino]-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-123);

7-methyl-2-(4-morpholinyl)-9-[(2-pyridinylmethyl)amino]-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-161);

9-[(4-chlorophenyl)methyl]amino]-7-methyl-2-(4-morpholinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-108);

2-(4-morpholinyl)-9-(phenylmethyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-040);

7-methyl-9-(*N*-Methyl-*N*-phenyl)aminomethyl-2-(4-morpholinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-195);

2-(4-morpholinyl)-8-(phenylmethyl)oxy-4H-1-benzopyran-4-one (TGX-102);

2-(4-morpholinyl)-8-(phenylmethyl)amino-4H-1-benzopyran-4-one (TGX-204);

2-(4-morpholinyl)-8-phenylamino-4H-1-benzopyran-4-one (TGX-324);

8-(3-chlorophenyl)oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one (TGX-259);

8-(3-methylphenyl)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-127);

8-(2-fluorophenyl)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-143);

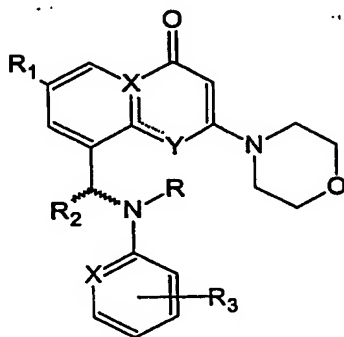
(±)-7-methyl-2-morpholin-4-yl-9-[1-(3-pyridinylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (KN-304).

3. The method of claim 2, wherein the selective PI 3-kinase  $\beta$  inhibitor is according to formula (I):

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(I)

wherein,

R is H, C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkyl, or aryl or (CH<sub>2</sub>)<sub>n</sub>-aryl;

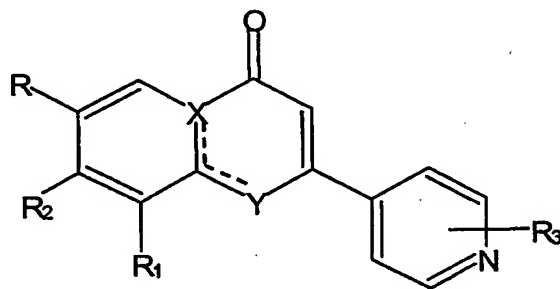
R<sub>1</sub> is H, OH, OCH<sub>3</sub>, OCF<sub>3</sub>, F, Cl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkyl, or aryl or (CH<sub>2</sub>)<sub>n</sub>-aryl;

R<sub>2</sub> is H, C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkyl, or aryl or (CH<sub>2</sub>)<sub>n</sub>-aryl in either the R or the S configuration

R<sub>3</sub> is one or more of H, F, Cl, Br, I, CN, CO<sub>2</sub>H, CO<sub>2</sub>R, NO<sub>2</sub>, CF<sub>3</sub>, substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCH<sub>3</sub>, OCH<sub>2</sub>F, OCHF<sub>2</sub>, OCF<sub>3</sub>, OR, OSO<sub>2</sub>-aryl, substituted or unsubstituted amine, NHCOR, NHSO<sub>2</sub>R, CONHR, or SO<sub>2</sub>NHR

X is C or N and Y is N or O.

4. The method of claim 2, wherein the selective PI 3-kinase  $\beta$  inhibitor is according to formula (III):



(III)

where X and Y are C and O respectively, or C and NH respectively, or both N.

R is H, OH, OCH<sub>3</sub>, OCF<sub>3</sub>, F, Cl, Br, I, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl or (CH<sub>2</sub>)<sub>n</sub>-aryl;

R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are independently H, OH, F, Cl, Br, I, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, CH=CH-aryl, C $\equiv$ C-aryl, (CHR'<sup>3</sup>)<sub>n</sub>-aryl, NR'<sup>3</sup>-C<sub>1</sub>-C<sub>6</sub> alkyl, NR'<sup>3</sup>-cycloalkyl, NR'<sup>3</sup>-(CHR'<sup>3</sup>)<sub>n</sub>-

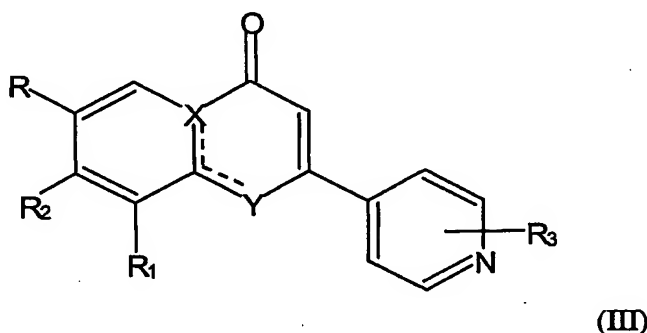
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aryl,  $(\text{CHR}^{\text{'3}})_n\text{-NR}^{\text{'3}}$ -aryl,  $(\text{CHR}^{\text{'3}})_n\text{-NR}^{\text{'3}}$ -alkyl,  $(\text{CHR}^{\text{'3}})_n\text{-NR}^{\text{'3}}$ -cycloalkyl,  $(\text{CHR}^{\text{'3}})_n\text{-O-aryl}$ ,  $(\text{CHR}^{\text{'3}})_n\text{-O-alkyl}$ ,  $(\text{CHR}^{\text{'3}})_n\text{-O-cycloalkyl}$ ,  $\text{O-}(\text{CHR}^{\text{'3}})_n\text{-aryl}$ ,  $\text{S-}(\text{CHR}^{\text{'3}})_n\text{-aryl}$ , or  $\text{CO-aryl}$ , wherein  $n$  is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN,  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{R}^{\text{'3}}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ , substituted or unsubstituted  $\text{C}_1\text{-C}_6$  alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl,  $\text{OCF}_3$ ,  $\text{OR}^{\text{'3}}$ ,  $\text{OSO}_2\text{-aryl}$ , substituted or unsubstituted amine,  $\text{NHCOR}^{\text{'3}}$ ,  $\text{NH}\text{SO}_2\text{R}^{\text{'3}}$ ,  $\text{CONHR}^{\text{'3}}$ , or  $\text{SO}_2\text{NHR}^{\text{'3}}$ ; and  $\text{R}^{\text{'3}}$  is H, or substituted or unsubstituted  $\text{C}_1\text{-C}_6$  alkyl, substituted or unsubstituted aryl.

5. A compound having the following formula (III):



where  $X$  and  $Y$  are C and O respectively, or C and NH respectively, or both N.

$R$  is H, OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ , F, Cl, Br, I,  $\text{C}_1\text{-C}_6$  alkyl, aryl or  $(\text{CH}_2)_n\text{-aryl}$ ;

$R_1$ ,  $R_2$  and  $R_3$  are independently H, OH, F, Cl, Br, I,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_3\text{-C}_6$  cycloalkyl,  $\text{CH=CH-aryl}$ ,  $\text{C}\equiv\text{C-aryl}$ ,  $(\text{CHR}^{\text{'3}})_n\text{-aryl}$ ,  $\text{NR}^{\text{'3}}\text{-C}_1\text{-C}_6$  alkyl,  $\text{NR}^{\text{'3}}\text{-cycloalkyl}$ ,  $\text{NR}^{\text{'3}}\text{-}(\text{CHR}^{\text{'3}})_n\text{-aryl}$ ,  $(\text{CHR}^{\text{'3}})_n\text{-NR}^{\text{'3}}$ -aryl,  $(\text{CHR}^{\text{'3}})_n\text{-NR}^{\text{'3}}$ -alkyl,  $(\text{CHR}^{\text{'3}})_n\text{-NR}^{\text{'3}}$ -cycloalkyl,  $(\text{CHR}^{\text{'3}})_n\text{-O-aryl}$ ,  $(\text{CHR}^{\text{'3}})_n\text{-O-alkyl}$ ,  $(\text{CHR}^{\text{'3}})_n\text{-O-cycloalkyl}$ ,  $\text{O-}(\text{CHR}^{\text{'3}})_n\text{-aryl}$ ,  $\text{S-}(\text{CHR}^{\text{'3}})_n\text{-aryl}$ , or  $\text{CO-aryl}$ , wherein  $n$  is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN,  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{R}^{\text{'3}}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ , substituted or unsubstituted  $\text{C}_1\text{-C}_6$  alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl,  $\text{OCF}_3$ ,  $\text{OR}^{\text{'3}}$ ,  $\text{OSO}_2\text{-aryl}$ , substituted or unsubstituted amine,  $\text{NHCOR}^{\text{'3}}$ ,  $\text{NH}\text{SO}_2\text{R}^{\text{'3}}$ ,  $\text{CONHR}^{\text{'3}}$ , or  $\text{SO}_2\text{NHR}^{\text{'3}}$ ; and

$\text{R}^{\text{'3}}$  is H, or substituted or unsubstituted  $\text{C}_1\text{-C}_6$  alkyl, substituted or unsubstituted aryl.

6. The method of claim 2, comprising administering the 2-morpholino-substituted derivative of formula (I) wherein:

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R is H, C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkyl or aryl;

R<sub>1</sub> is H, OH, OCH<sub>3</sub>, OCF<sub>3</sub>, F, Cl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkyl;

R<sub>2</sub> is H, C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkyl, or aryl in either the R or the S configuration

R<sub>3</sub> is one or more of H, F, Cl, Br, CN, CO<sub>2</sub>H, CO<sub>2</sub>R, NO<sub>2</sub>, CF<sub>3</sub>, branched or straight chain C<sub>1</sub>-C<sub>6</sub> alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCH<sub>3</sub>, OCH<sub>2</sub>F, OCHF<sub>2</sub>, OCF<sub>3</sub>, OR, substituted or unsubstituted amine, NHCOR, NHSO<sub>2</sub>R, CONHR, or SO<sub>2</sub>NHR

X is C or N and Y is N or O.

7. The method of claim 2, wherein the inhibitor administered is selected from the group consisting of:

(±)-7-methyl-9-([methyl(phenyl)amino]methyl)-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-195);

(±)-7-methyl-2-morpholin-4-yl-9-(1-phenylaminoethyl)-pyrido[1,2-a]pyrimidin-4-one (TGX-221);

(±)-7-methyl-2-morpholin-4-yl-9-[1-(4-fluorophenylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-224);

(±)-9-[1-(3,4-difluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-237);

(±)-9-[1-(2,5-difluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-238);

(±)-9-[1-(3,5-difluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-239);

(±)-9-[1-(4-fluoro-2-methylphenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-240);

(±)-9-[1-(4-chlorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-243);

(±)-9-[1-(3,4-dichlorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-244);

(±)-9-[1-(3-fluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-247);

(±)-9-[1-(3-chlorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-248);

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(±)-7-methyl-2-morpholin-4-yl-9-[1-(2-thiazolylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-261);

(±)-7-methyl-9-[1-(3-methylphenylamino)ethyl]-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-262);

(±)-7-methyl-2-morpholin-4-yl-9-[1-(3-trifluoromethylphenylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-264); and

(±)-7-methyl-2-morpholin-4-yl-9-[1-(2-pyridinylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-295).

(±)-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzoic acid (KN-309);

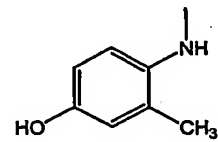
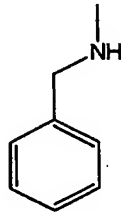
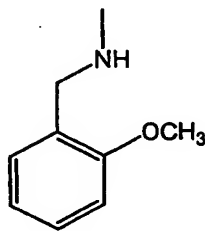
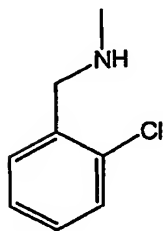
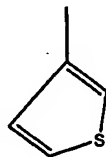
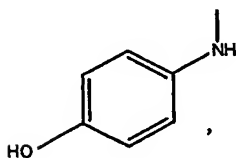
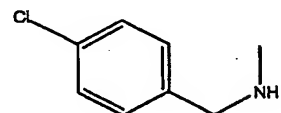
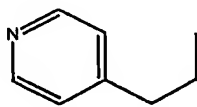
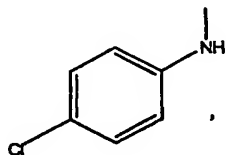
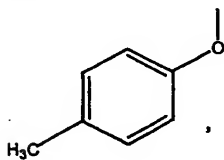
(±) methyl 2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzoate (KN-321);

(±)-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzonitrile (KN-320);

(±)-7-methyl-2-(morpholin-4-yl)-9-(1-{[2-(2H-tetrazol-5-yl)phenyl]amino}ethyl)-pyrido[1,2-a]pyrimidin-4-one (KN-325);

(±)-2-(4-morpholinyl)-8[1-(phenylamino)ethyl]-4H-1-benzopyran-4-one (TGX-280).

8. The compound of claim 5, wherein R<sup>1</sup> is selected from a group consisting of, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>,

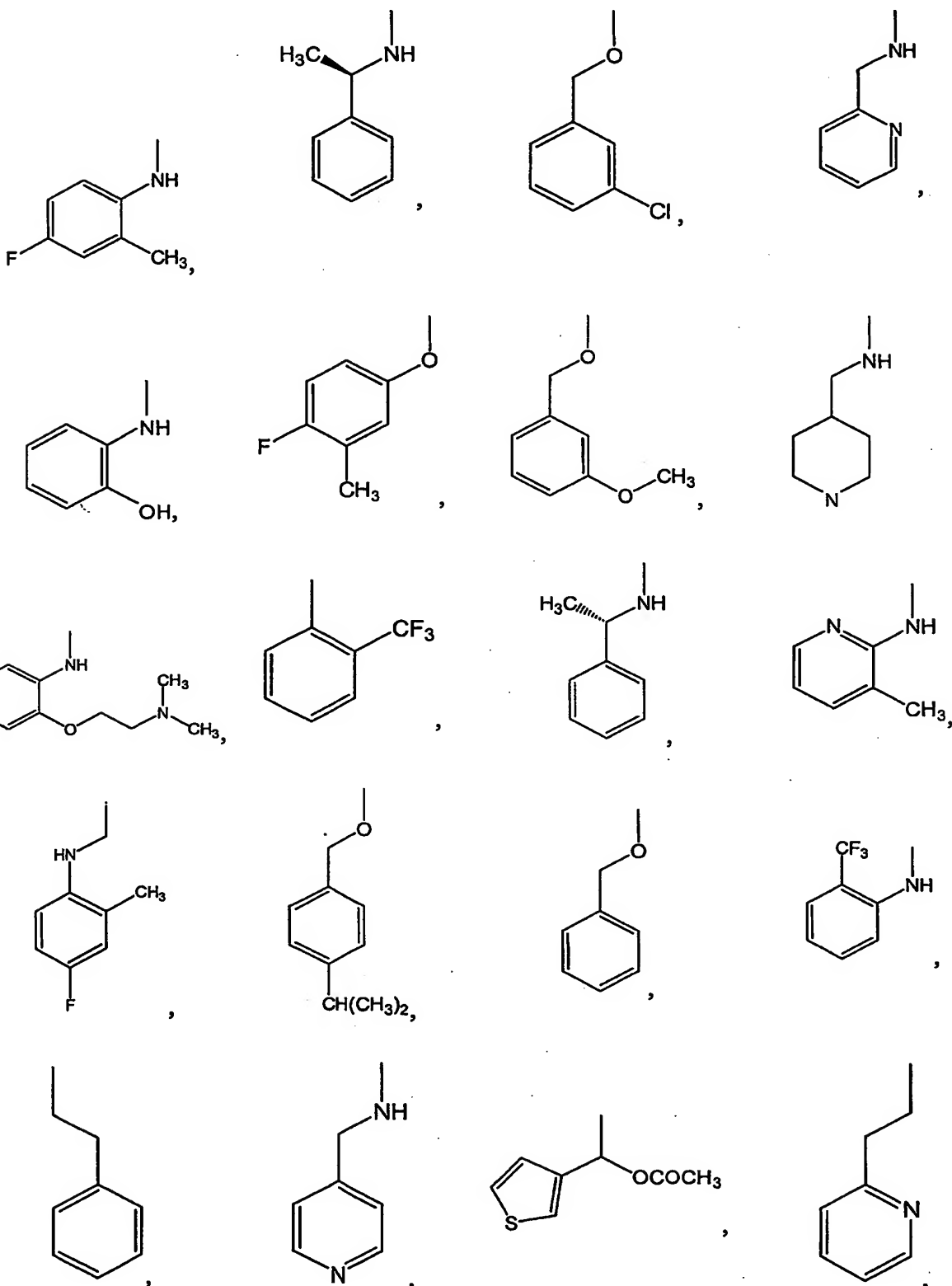


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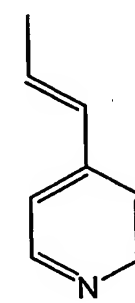
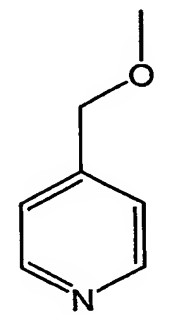
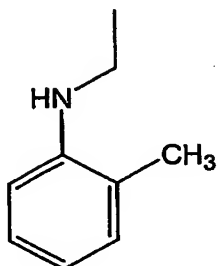
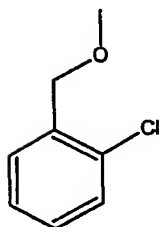
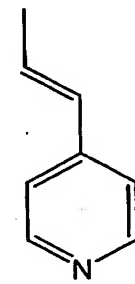
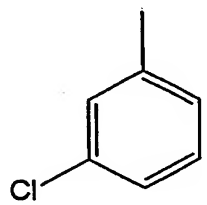
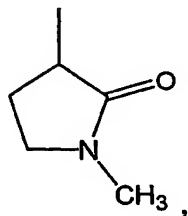
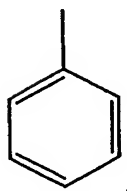
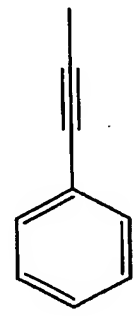
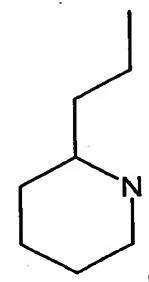
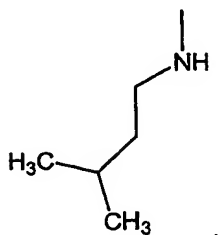
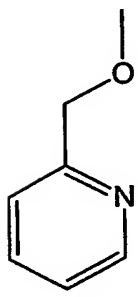
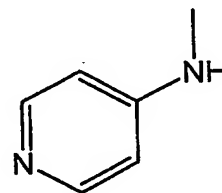
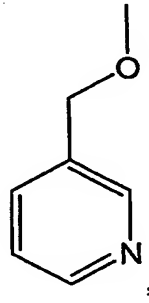
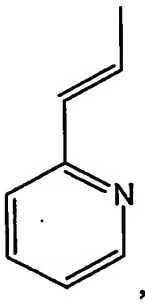
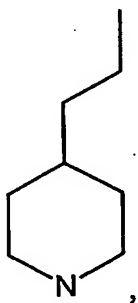


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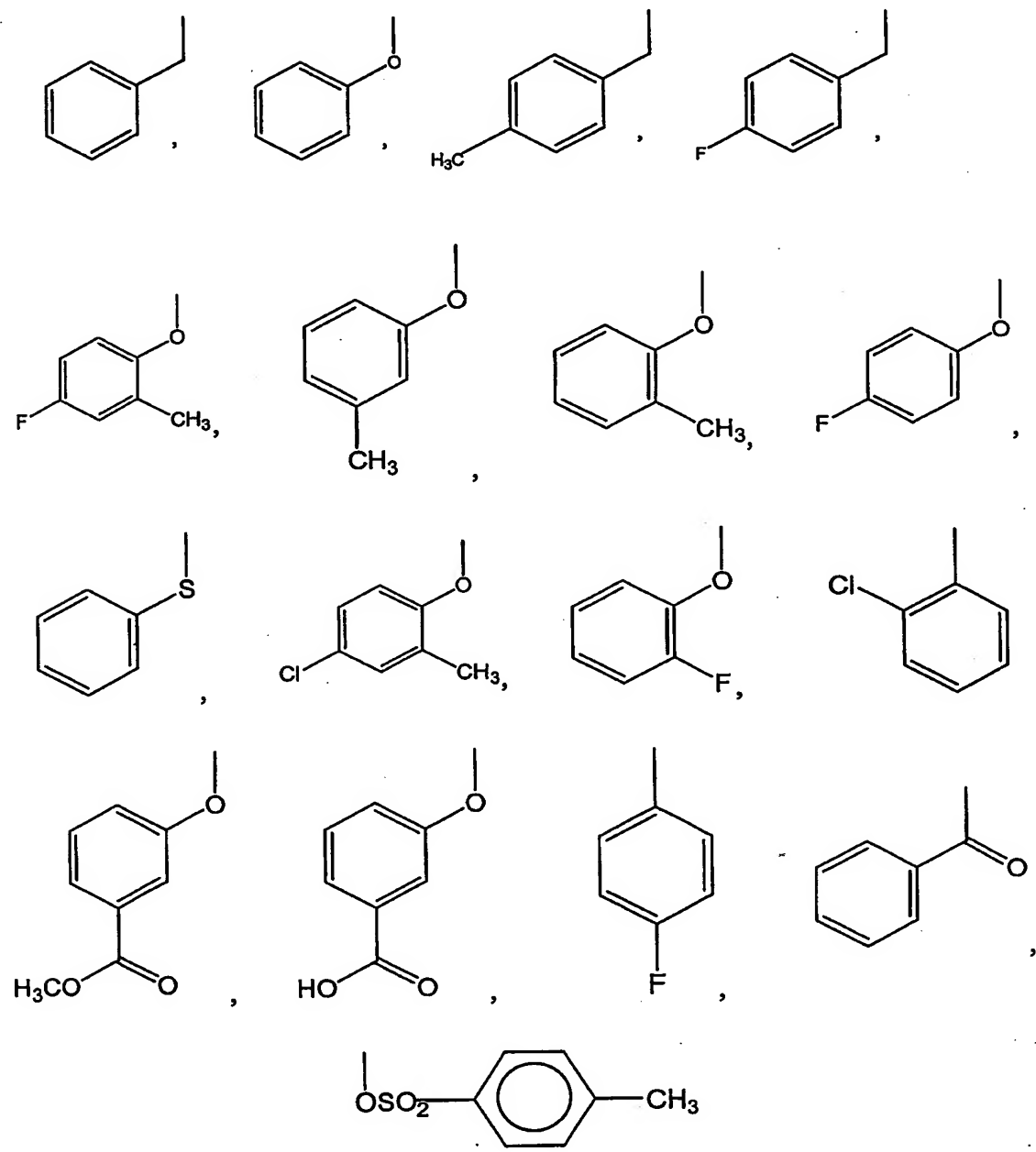


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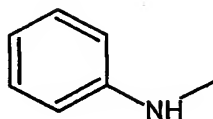
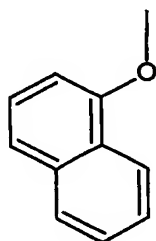
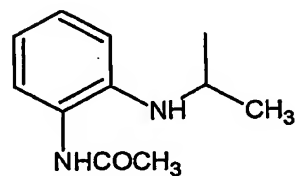
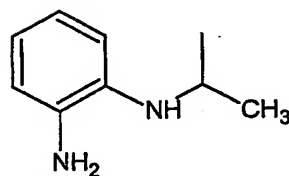
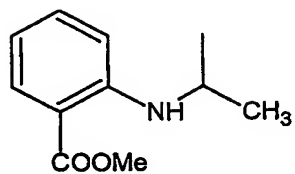
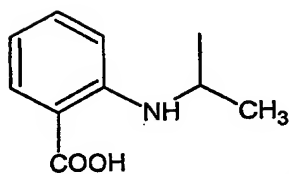
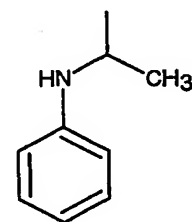
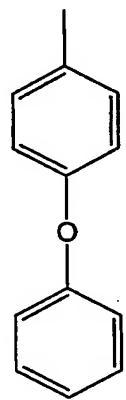
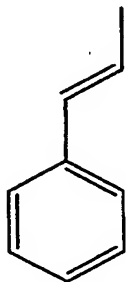
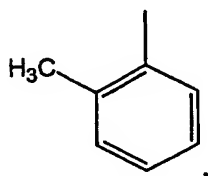
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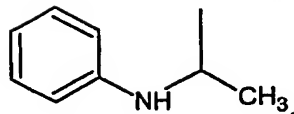
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9. The compound of claim 5, wherein R is methyl and  $\text{R}^1$  is

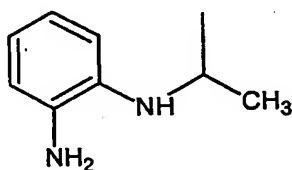


10. The compound of claim 5, wherein R is methyl and  $\text{R}^1$  is

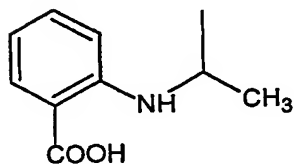
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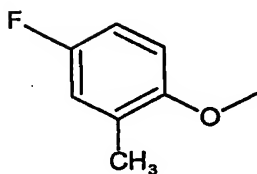
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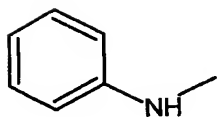
11. The compound of claim 5, wherein R is methyl and  $\text{R}^1$  is



12. The compound of claim 5, wherein R is H and  $\text{R}^1$  is



13. The compound of claim 5, wherein R is H and  $\text{R}^1$  is



14. A method for inhibiting phosphoinositide 3-kinase in a patient, comprising administering to a patient an amount of the compound of claim 5 effective in inhibiting the phosphoinositide 3-kinase in the patient.

15. A method for preventing or treating cardiovascular disease comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

16. A method for preventing or treating respiratory disease comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

17. A method for preventing or treating cancer comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

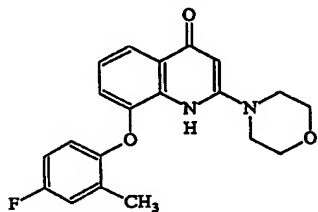
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18. A method for preventing or treating disease linked to disordered white blood cell function comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

19. The method of claim 2, wherein the inhibitor administered is:



20. The method of claim 4, wherein the inhibitor administered is 6-methyl-8-[1-(phenylamino)ethyl]-2-(4-pyridinyl)-4H-benzopyran-4-one.

21. The method of claim 4, wherein the inhibitor administered is 6-methyl-8-[1-[(2-aminophenyl)amino]ethyl]-2-(4-pyridinyl)-4H-benzopyran-4-one.

22. A compound which is ( $\pm$ )-7-methyl-2-morpholin-4-yl-9-(1-phenylaminoethyl)-pyrido[1,2-a]pyrimidin-4-one.

23. A compound which is ( $\pm$ )-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl} amino)benzoic acid.

24. A compound which is ( $\pm$ )-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl} amino)benzonitrile.

25. A compound which is ( $\pm$ ) methyl 2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl} amino)benzoate.

26. A compound which is ( $\pm$ )-7-methyl-2-(morpholin-4-yl)-9-(1-{[2-(2H-tetrazol-5-yl)phenyl]amino}ethyl)-pyrido[1,2-a]pyrimidin-4-one.